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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 02/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,664	BEN-BASSAT ET AL.	
	Examin r	Art Unit	
	David J Steadman	1652	

-- Th MAILING DATE of this communication appears n the cov r sh et with th correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/11 10/18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

[1] Claims 1-20 are pending in the application.

Election/Restriction

[2] Applicants' election without traverse of the invention of Group IX, claims 12-17 and 19-20, filed December 29, 2003, is acknowledged.

[3] Claims 1-11 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

[4] Claims 12-17 and 19-20 are being examined on the merits.

Information Disclosure Statement

[5] All references cited by applicants in the information disclosure statements (IDSs) filed July 11, 2002 and October 18, 2002 have been considered by the examiner. A copy of each IDS is attached to the instant Office action.

[6] As stated in a previous Office action, the information disclosure statement filed March 20, 2002 fails to comply with 37 CFR 1 .98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. See item 2 of the Office action mailed November 26, 2003.

Oath/Declaration

[7] The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because: Non-initialed and/or non-dated alterations for applicant K. Gibson have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification/Informalities

[8] As stated in a previous Office action, applicants' claim to domestic priority under 35 U.S.C. 121 in the first of the specification and the application data sheet is acknowledged - however, the status of the nonprovisional parent applications (whether patented or abandoned) should also be included (see item 3 of the Office action mailed November 26, 2003). If a parent application has become a patent, the expression "now Patent No. " should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

[9] The specification is objected to as there is disclosed a description of Figure 8 (page 5), however, there is no Figure 8 in the drawings submitted November 28, 2001. It is suggested that applicants correct this discrepancy in the specification/drawings.

[10] The specification is objected to as there is disclosed descriptions of SEQ ID NO:1-142 (pages 6-7), however, the paper copy of the sequence listing submitted November 28, 2001 provides only the nucleic acid and amino acid sequences of SEQ

ID NO:1-112. It is suggested that applicants correct this discrepancy in the specification/sequence listing.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[11] Claim(s) 12-17 and 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[12] Claim 12 (claims 13-17 and 19-20 dependent therefrom) is confusing in the recitation of "recovering the p-hydroxybenzoate produced in (ii)". Step (ii) recites "at least one fermentable carbon substrate" and does not recite a method step for the production of p-hydroxybenzoate. It appears that part (c) of claim 12 should depend from part (b) and the claim has been examined accordingly. It is suggested that applicant clarify the meaning of the claim.

[13] Claim 12 (claims 13-17 and 19-20 dependent therefrom) is indefinite in the recitation of "compounds degraded by the toluene monooxygenase enzyme pathway". The specification discloses, "[t]he term "aromatlc organlc substrate" refers to an aromatic compound that is degraded by the TMO enzymatic pathway. Typical examples of suitable aromatic substrates are toluene, p-cresol, p-hydroxybenzyl, and p-hydroxybenzaldehyde" (page 9, top). However, based on this definition, there is no way to distinguish those substrates that are meant to be included in the term and those that

are meant to be excluded. It is suggested that applicants specifically identify those substrates that are intended to be encompassed by the term.

[14] Claim 12 (claims 13-17 and 19-20 dependent therefrom) is indefinite in the recitation of "genes encoding... TmoX... activities" in part (iii) of the claim. The examiner can find no disclosure of the activity of a TmoX polypeptide and it is unclear as to applicants' intended biological activity. It is suggested that applicant direct the examiner's attention to the specification wherein the activity of TmoX is described and/or clarify the meaning of the claim.

[15] Claim 20 is confusing as the transformed host cell of claim 12 from which claim 20 is dependent upon already comprises genes encoding TmoST polypeptides, which presumably have TmoST activity. It is suggested that applicants clarify the meaning of the claim.

[16] Claim 20 recites the limitation "the genes encoding TmoST activity". There is insufficient antecedent basis for this limitation in the claim. It is suggested that applicants clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[17] Claims 12-17 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

The claims are drawn to a method for the production of para-hydroxybenzoate comprising the steps of: (a) contacting a genus of transformed host cells with a medium comprising: (i) an aromatic organic substrate selected from toluene, para-cresol, para-hydroxybenzyl alcohol, para-hydroxybenzaldehyde, or a genus of aromatic compounds degraded by the toluene monooxygenase enzyme pathway; (ii) a fermentable carbon substrate; and (iii) a nitrogen source, wherein the transformed host cell is (1) lacking a para-hydroxybenzoate hydroxylase activity and (2) comprises a genera of genes encoding toluene-4-monooxygenase, TmoX, PcuR, para-cresol methylhydroxylase, TmoS, TmoT, and para-hydroxybenzoate dehydrogenase; (b) incubating the transformed host cell for a time sufficient to produce para-hydroxybenzoate; and (c) optionally recovering the para-hydroxybenzoate produced in step (b).

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such

identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses methods of producing para-hydroxybenzoate using only three representative host cells, *i.e.,* *Pseudomonas putida, Pseudomonas mendocina,* or *Agrobacterium rhizogenes* host cell that does not express para-hydroxybenzoate hydroxylase or has an inactivated gene encoding endogenous para-hydroxybenzoate hydroxylase and comprises a nucleic acid encoding a naturally-occurring *Pseudomonas mendocina* KR1 toluene-4-monooxygenase, a nucleic acid encoding the TmoX polypeptide of SEQ ID NO:92, a nucleic acid encoding the PcuR polypeptide of SEQ ID NO:2, a nucleic acid encoding a naturally occurring *Pseudomonas* para-cresol methylhydroxylase, a nucleic acid encoding the TmoS polypeptide of SEQ ID NO:116, a nucleic acid encoding the TmoT polypeptide of SEQ ID NO:117, and a nucleic acid encoding a naturally occurring *Pseudomonas* para-hydroxybenzoate dehydrogenase with the ability to convert toluene, para-cresol, para-hydroxybenzyl alcohol, or para-hydroxybenzaldehyde to para-hydroxybenzoate. The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which

embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of transformed host cells having the ability to convert all aromatic compounds degraded by the toluene monooxygenase enzyme pathway into para-hydroxybenzoate encompasses species that are WIDELY variant. As such, the disclosure of the representative species as stated above is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of recited transformants and substrates acted on thereby. Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[18] Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ the novel plasmid, pMC4. Since the plasmid is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The recited plasmid's sequence is not fully disclosed, nor have all the sequences required for its construction been shown to be publicly known and freely available. *The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the plasmid.* The specification does not disclose a repeatable process to obtain the vectors and it is not

apparent if the plasmid sequence is readily available to the public. Accordingly, it is deemed that a deposit of this plasmid should have been made in accordance with 37 CFR 1.801-1.809.

If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. During the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

2. All restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

3. The deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

4. The deposit will be replaced if it should ever become inviable.

[19] Even if applicant satisfies the requirements of 35 USC 112, first paragraph by depositing the recited plasmid, the following rejection including claim 19 still applies.

[20] Claim(s) 12-17 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of para-hydroxybenzoate comprising the steps of: (a) contacting a transformed *Pseudomonas putida, Pseudomonas mendocina,* or *Agrobacterium rhizogenes* host cell with a medium comprising: (i) an aromatic organic substrate selected from toluene, para-cresol, para-hydroxybenzyl alcohol, or para-hydroxybenzaldehyde; (ii) a fermentable carbon substrate; and (iii) a nitrogen source, wherein the transformed host cell (1) does not express para-hydroxybenzoate hydroxylase or has an inactivated gene encoding endogenous para-hydroxybenzoate hydroxylase and (2) comprises a nucleic acid encoding a naturally-occurring *Pseudomonas mendocina* KR1 toluene-4-monooxygenase, a nucleic acid encoding the TmoX polypeptide of SEQ ID NO:92, a nucleic acid encoding the PcuR polypeptide of SEQ ID NO:2, a nucleic acid encoding a naturally occurring *Pseudomonas* para-cresol methylhydroxylase, a nucleic acid encoding the TmoS polypeptide of SEQ ID NO:116, a nucleic acid encoding the TmoT polypeptide of SEQ ID NO:117, and a nucleic acid encoding a naturally occurring *Pseudomonas* para-hydroxybenzoate dehydrogenase; (b) incubating the transformed host cell for a time sufficient to produce para-hydroxybenzoate; and (c) optionally recovering the para-hydroxybenzoate produced in step (b), does not reasonably provide enablement for a method for the production of para-hydroxybenzoate comprising the steps of: (a) contacting *any* transformed host cell with a medium comprising: (i) an

aromatic organic substrate selected from toluene, para-cresol, para-hydroxybenzyl alcohol, para-hydroxybenzaldehyde, or *any* aromatic compound degraded by the toluene monooxygenase enzyme pathway; (ii) a fermentable carbon substrate; and (iii) a nitrogen source, wherein the transformed host cell is (1) lacking a para-hydroxybenzoate hydroxylase activity by *any* means and (2) comprises genes encoding *any* toluene-4-monooxygenase, *any* TmoX polypeptide, *any* PcuR polypeptide, *any* para-cresol methylhydroxylase, *any* TmoS polypeptide, *any* TmoT polypeptide, and *any* para-hydroxybenzoate dehydrogenase; (b) incubating the transformed host cell for a time sufficient to produce para-hydroxybenzoate; and (c) optionally recovering the para-hydroxybenzoate produced in step (b). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP §

2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass a method for the production of para-hydroxybenzoate comprising the steps of: (a) contacting *any* transformed host cell with a medium comprising: (i) an aromatic organic substrate selected from toluene, para-cresol, para-hydroxybenzyl alcohol, para-hydroxybenzaldehyde, or *any* aromatic compound degraded by the toluene monooxygenase enzyme pathway; (ii) a fermentable carbon substrate; and (iii) a nitrogen source, wherein the transformed host cell is (1) lacking a para-hydroxybenzoate hydroxylase activity by *any* means and (2) comprises genes encoding *any* toluene-4-monooxygenase, *any* TmoX polypeptide, *any* PcuR polypeptide, *any* para-cresol methylhydroxylase, *any* TmoS polypeptide, *any* TmoT polypeptide, and *any* para-hydroxybenzoate dehydrogenase; (b) incubating the transformed host cell for a time sufficient to produce para-hydroxybenzoate; and (c) optionally recovering the para-hydroxybenzoate produced in step (b). The broad scope of recited transformed host cells and substrates is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. In this case the disclosure is limited to a method for the production of para-hydroxybenzoate comprising the steps of: (a) contacting a transformed *Pseudomonas putida, Pseudomonas mendocina,* or *Agrobacterium rhizogenes* host cell with a medium comprising: (i) an aromatic organic substrate selected from toluene, para-cresol, para-hydroxybenzyl alcohol, or para-

hydroxybenzaldehyde; (ii) a fermentable carbon substrate; and (iii) a nitrogen source, wherein the transformed host cell (1) does not express para-hydroxybenzoate hydroxylase or has an inactivated gene encoding endogenous para-hydroxybenzoate hydroxylase and (2) comprises a nucleic acid encoding a naturally-occurring *Pseudomonas mendocina* KR1 toluene-4-monooxygenase, a nucleic acid encoding the TmoX polypeptide of SEQ ID NO:92, a nucleic acid encoding the PcuR polypeptide of SEQ ID NO:2, a nucleic acid encoding a naturally occurring *Pseudomonas* para-cresol methylhydroxylase, a nucleic acid encoding the TmoS polypeptide of SEQ ID NO:116, a nucleic acid encoding the TmoT polypeptide of SEQ ID NO:117, and a nucleic acid encoding a naturally occurring *Pseudomonas* para-hydroxybenzoate dehydrogenase; (b) incubating the transformed host cell for a time sufficient to produce para-hydroxybenzoate; and (c) optionally recovering the para-hydroxybenzoate produced in step (b).

- The lack of guidance and working examples: The specification provides only three working example of the claimed method *i.e.*, Examples 9-12 as set forth at pages 47-49 of the instant specification. These working examples fail to provide the necessary guidance for making the entire scope of claimed methods. The specification fails to provide guidance for isolating genes encoding *all* toluene-4-monooxygenases, TmoX polypeptides, PcuR polypeptides, para-cresol methylhydroxylases, TmoS polypeptides, TmoT polypeptides, and para-hydroxybenzoate dehydrogenases, which encompasses open reading frames and regulatory sequences, including nucleic acids encoding mutant and variants thereof.

- The high degree of unpredictability in the art: While the prior art acknowledges the isolation of nucleic acids encoding toluene-4-monooxygenase from *Pseudomonas mendocina* KR1 (see, *e.g.,* Yen et al. *J Bacteriol* 1735315-5327; cited in the IDS filed June 11, 2002), para-cresol methylhydroxylase from *Pseudomonas* (see *e.g.,* Kim et al. *J Bacteriol* 176:6349-6361; cited in the IDS filed October 18, 2002), and para-hydroxybenzoate dehydrogenase. However, there is no indication in the specification that genes encoding all other toluene-4-monooxygenases, para-cresol methylhydroxylases, and para-hydroxybenzoate dehydrogenase have sequences that are so similar that these sequences can be isolated using those genes known in the art. Also, while the specification teaches the production of PHBA using *Pseudomonas putida, Pseudomonas mendocina,* or *Agrobacterium rhizogenes* as a host, there is no indication in the specification or prior art that *all* other bacterial strains are so useful and it is highly unpredictable as to whether any other bacteria can be used for this purpose, *e.g.*, are other bacteria able to maintain viability in the presence of other organic aromatic compounds such as toluene? Furthermore, the claims encompass mutants and variants of those genes encoding toluene-4-monooxygenases, para-cresol methylhydroxylases, and para-hydroxybenzoate dehydrogenase that are and are not known in the art. The encoding nucleic acid sequence for a given polypeptide determines the protein's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e.,

expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability in making the entire scope of polypeptides having the desired activity.

- The state of the prior art supports the high degree of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein.

Such mutations may even completely alter a protein's activity. Also, regarding the use of *any* bacteria for practicing the claimed method, it is noted that Ramos-Gonzalez et al. (*Appl Eviron Microbiol* 69:5120-5127) teach that a highly solvent resistant strain of *Pseudomonas putida* was used for bioconversion of toluene to para-hydroxybenzoate. Other bacterial strains are not so solvent resistant and it would appear that the method is not applicable to all such bacterial hosts, *e.g., E. coli* or *B. subtilis.*

- The amount of experimentation required is undue: While methods of isolating variants of a gene encoding a given polypeptide, *e.g.*, by site-directed mutagenesis, and methods of isolating variants of protein-encoding polynucleotides, *e.g.*,, hybridization, are known, it is not routine in the art to screen for *all* polypeptide-encoding genes having a substantial number of modifications, as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is

unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting Rejection(s)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[21] Claims 12-17 and 19-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14, 16-19, and 22-26 of copending US Application 10/464,952 (Application '952). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the instant application and the claims of Application '952 are directed to a

method for the production of para-hydroxybenzoate. The claims differ in that the transformed host cell of claim 12 of the instant application comprises genes encoding TmoST polypeptides. The specification of Application '952 supports an embodiment that would anticipate claims 12-17 and 19-20 herein, *i.e.*, the use of a transformed *Pseudomonas mendocina* host cell for para-hydroxybenzoate production (see, *e.g.*, see page 9, paragraph [0130] and of US 2003/0207322 A1, which is the published version of Application '952), as *Pseudomonas mendocina* endogenously expresses TmoST polypeptides (see page 24, bottom of the instant application). Furthermore, it is noted that claim 26 of Application '952 limits the host cell of claim 14 of Application '952 to further comprising genes encoding TodST activity. The specification Application '952 defines the activity of TodST as being transcriptional activators of enzymes involved in the toluene monooxygenase pathway (see page 21, paragraph [0244] of Application '952), which is identical to the definition provided for the activities of TomST polypeptides as provided in the specification of the instant application (see page 24, lines 29-31). Therefore, there appears to be no difference between the activities of TodST and TomST polypeptides. Claims 12-17 and 19-20 of the instant application cannot be considered to be patentably distinct over claims 14, 16-19, and 22-26 of Application '952 when there are specifically recited embodiments in Application '952 that would anticipate claims 12-17 and 19-20 of the instant application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Relevant Art

[22] The following reference is made of record in the instant application. It is noted that this reference is NOT prior art as it was published after the filing date of the instant application. The relevant reference is Ramos-Gonzalez et al. *J Bacteriol* 184:7062-7067. The reference is relevant to the instant application as it discloses the initial isolation and characterization of *Pseudomonas mendocina* TmoST polypeptides.

Conclusion

[23] Status of the claims:

- Claims 1-20 are pending.
- Claims 1-11 and 18 are withdrawn from consideration.
- Claims 12-17 and 19-20 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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01-29-04
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